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REVIEW ARTICLE

Mechanisms of Radiation Bystander and Non-Targeted Effects: Implications to Radiation Carcinogenesis and Radiotherapy

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Abstract: ***Background:*** Knowledge of radiobiology is of paramount importance to be able to grasp and have an in-depth understanding of the consequences of ionizing radiation. One of the most important effects of this physical stressor's interaction to targeted and non-targeted cells, tissues and organs is on the late effects on the development of primary and secondary cancers. Thus, an in-depth understanding of the mechanisms of radiation carcinogenesis remains to be elucidated, and some studies have demonstrated or proposed a role of non-targeted effect in excess risk of cancer incidence. The non-targeted effect in radiobiology refers to a dynamic complex response in non-irradiated tissues caused by the release of presumably of clastogenic factors from irradiated cells. Although, most of these responses in non-targeted tissues have marked similarities to irradiated tissues, other studies have shown some differences. Also, the non-targeted effect has shown sex and tissue specificity that are seen in irradiated tissues too. So far, several studies have been conducted to depict mechanisms that may be involved in this phenomenon. Epigenetic dysfunctions, DNA damage and cell death are responsible for initiation of several signaling pathways that finally result in secretion of clastogenic factors. Moreover, studies have shown that damage to both nucleus and mitochondrial DNA, membrane and some organelles is involved. Oxidized DNA associated with other cell death factors stimulates secretion of inflammatory as well as some anti-inflammatory cytokines from irradiated area. Additionally, oxidative stress that results in damage to cellular structures to include cell membranes can affect secretion of exosomes and miRNAs. These bystander effect exogenous mediators migrate to distant tissues and stimulate various signaling pathways which can lead to changes in immune responses, epigenetic modulations and radiation carcinogenesis.

Conclusion: In this review, we focus on descriptive and hierarchical events with emphasis on the molecular and functional interactions of ionizing radiation with cells to the mechanisms involved in cancer induction in non-targeted tissues.

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1. INTRODUCTION

Irradiation of cells and tissues generates a series of processes that occur in nanoseconds. The first event is the biophysical interaction between radiation and cells. The collision between radiation and atoms of viable cells results in the ejection of the electrons and ionization. The ionization event is the first step that induces damage in the cells resulting from unstable molecules and cellular and molecular triggered malfunctions. For many years it has been accepted that the DNA is the most critical target for the interaction of ionizing radiation and its produced free radicals. Moreover, it was accepted that DNA damage occurs instantaneously after radiation interaction. In the last two decades, the classical nuclear target paradigm of radiation biology is challenged by the non-targeted effect of radiation. This phenomenon has been widely investigated by several scientists, to include the effects of ionizing radiation that is seen in the cells or tissues

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that are not directly exposed to ionizing radiation track [1]. This phenomenon results in systemic DNA damage and also in some abnormal changes in the cell functions following local irradiation [2-4].

There are some suggestions that non-targeted effect causes permanent changes in DNA structure that can be transferred to the succeeding generations as well [5-7]. Evaluating epigenetic landmarks has shown that local irradiation results in hypomethylation, and also in upregulation or downregulation of some microRNAs (miRNAs) in non-targeted tissues. Upregulation and downregulation of miRNAs involved in the expression of oncogenes and tumor suppressor genes such as let-7 miRNAs may increase the risk of malignancies. Although, epigenetic changes depend on sex, irradiated and non-targeted organs and tissues [8-10].

Another important change in non-targeted tissues that may be linked to secondary carcinogenesis is the increased level of some inflammatory cytokines [11]. Inflammation has a direct link to carcinogenesis [12]. Increased inflammatory markers are associated with continuous reactive oxygen species (ROS) and nitric oxide (NO-) production which result in chromosome aberrations and genomic instability [13-15]. Moreover, it seems that there is a direct connection of inflammation and epigenetic changes [16, 17].

Radiation-induced carcinogenesis potential and non-targeted effects were studied by Mancuso *et al.* They showed that irradiation of shielded brains Ptch1+/− mice resulted in increased incidence of medulloblastoma. Elevated incidence of this cancer was associated with DNA damage including double strand break (DSB) and chromosome-13 interstitial deletions in actively dividing cells [18]. Analysis of the second primary cancer among people that have had radiotherapy for cancer has shown that abnormally increased cancer in out of filed organs may be related to non-targeted effect [19-22].

In view of these observations, radiotherapy for cancer is now being done localized as in external radiotherapy or brachytherapy, with the view that systemic effects of radiation increase concerns for potential carcinogenesis in distant tissues. As secondary malignancies affect cost-effectiveness, the therapeutic efficacy and value of radiotherapy, it is important to consider all factors that may influence the risk of radiation induced carcinogenesis [23]. This issue is more important for pediatric radiotherapy because of their higher radiosensitivity, and life expectancy for children. Some studies revealed up to 23 fold excess risk of secondary brain malignancy in children treated with radiotherapy [24, 25]. One study has shown that that risk of the second primary cancers is 10-fold for children in comparison with adults [26].

Bystander responses have been investigated in targeted radionuclide therapy. Boyd *et al.* in an *in vitro* experiment studied bystander effect for both external beam irradiation and exposure to 3 different radionuclides. They used a β-, auger electron, and α-emitter radionuclides in human glioma and bladder carcinoma cell lines. Their result indicated that bystander effect for radionuclides with higher LET auger electron and α-particle was more obvious compared to electron irradiation [27]. Incidence of *in vivo* bystander responses for tumor bearing mice that injected with ^{125}IUdR-labeled tumor cells has also been confirmed [28].

2. MOLECULAR BASES OF RADIATION INTERACTIONS:

2.1. Radiation-Induced DNA Damage, Cell Death and Tissue Injury

Although a complete description of the mechanisms involved in radiation bystander-non-targeted effect is missing, it seems that direct and indirect DNA-mediated damage responses, and its consequences following cell injury or death in the initial irradiated target area are primarily responsible for DNA damage and genomic instability in non-targeted cells. As DNA damage and genomic instability have a direct link to carcinogenesis, the non-targeted effect may increase the risk of second primary malignancies [29]. In addition to the increased risk of second malignancies, some studies have reported that non-targeted effect can result in normal tissue injury [30, 31].

DNA is the most critical target for ionizing radiation or free radical production. In addition to nuclear DNA, ionizing radiation can to break mitochondrial DNA and disrupt its normal function through the production of free radicals. Indirect generation of free radicals interacts with DNA, membrane, lipids and proteins. Oxidation of these macromolecules results in direct DNA damage, increasing membrane permeability and thus changing normal function of cells [32]. Massive DNA damage that is seen following exposure to clinical doses of ionizing radiation causes cellular death, either thru apoptosis, mitotic catastrophe, and necrosis and autophagy. Among these, cell death mechanisms, necrosis and apoptosis stimulate immune system responses through secretion of danger alarms. These signals known as damage-associated molecular patterns (DAMPs) are recognized through pattern recognition receptor (PRRs) [33, 34]. The most known PRRs in this pathway are named as toll like receptors (TLRs). Although several TLRs are known, it seems that TLR2, TLR4 and TLR9 are most important PRRs in response to cell death after irradiation [35]. These PRRs upregulate the expression of transcription factors such as NF-κB, STAT-1, STAT-3 and smad2 that result in secretion of various cytokines from immune cells [35, 36]. The role of sensitive molecular signaling and molecular receptors in radiation-mediated cell deaths and cell injury needs further understanding of their functions in correlating their utility for clinical radiotherapy and drug and gene targeted therapeutics discovery and applications.

2.2. Role of Cytoplasm and Membrane

Although DNA is the most critical target for radiation injury in cells, emerging evidence have proposed that irradiation of cytoplasm can lead to damage to direct irradiated or bystander cells. Several years ago, it has been reported that irradiation of cytoplasm can cause generation of toxin agents that are able to diffuse into the non-irradiated nucleus, leading to inhibition of DNA synthesis [37]. Nowadays, microbeam irradiation studies can identify biological response of cytoplasm after localized irradiation. Prise *et al.* showed that localized cytoplasm irradiation with alpha particles can cause induction of DNA damage in irradiated and bystander cells. They showed that DNA damage in bystander effect can be identified from 1 h to 3 h after irradiation. Also, their results showed that the inhibition of mitochondria attenuates

free radical production and DNA damage in bystander cells. In conclusion, their results indicated that the irradiation of cytoplasm through stimulation of mitochondria can trigger the production of ROS and NO in non-irradiated cells. Moreover, this study showed that induction of bystander effect in non-irradiated cell is independent of the number of irradiated cells or the numbers of alpha particles. Also it has been shown that bystander responses are independent of whether cytoplasm or nucleus irradiates with alpha particles [38]. This group showed that when one alpha particle irradiated to cytoplasm of glioma cells, the formation of micronuclei is increased in non-irradiated glioma or fibroblast cells. The formation of micronuclei was more obvious by twofold for fibroblast cells. Their results confirmed that NO has a key role in DNA damage in non-irradiated cells [39].

Exosome is another cytoplasmic mediator that is involved in bystander responses. Exosomes are microvesicles and nanovesicles secreted from both normal and tumor cells which have the potential to modulate cellular processes in other cells through intercellular signaling. Exosomes can be released from the plasma membrane and are involved in the removal of many plasma membrane proteins. These vesicles contain several types of messengers such as proteins, mRNAs, microRNAs and DNA fragments. The content of exosomes and their influence on other cells highly depend on the damaged cell type. Exposure to ionizing radiation leads to the release of exosomes from irradiated cells. The frequency of secreted exosomes correlates with the dead cells [40]. Since the exosomes have a small size, they influence cell function at distant tissues by traveling throughout the body [41]. One of the most important effects of exosomes is ROS production and DNA damage in other cells. Dutta *et al*. showed that secreted exosomes from breast cancer cells are able to produce ROS production and DNA damage in other cells [42]. Induction of DNA damage response following exposure to exosome has been demonstrated [43]. Ionizing radiation is able to change the composition of secreted exosomes. It has been shown that ionizing radiation induces the secretion of 236 proteins and suppress the secretion of 69 proteins from head and neck squamous cell carcinoma [44]. The number of released exosomes has also a direct relation to radiation dose [45]. In addition to proteins' content, ionizing radiation changes secreted exosome RNAs from irradiated cells. Also, it has been shown that RNA and protein molecules that transfer through exosomes to non-irradiated cells have a synergistic effect on induction of bystander effect [46]. Although complete mechanisms of induction of bystander effect through exosomes in bystander cells remain to be demonstrated, some mechanisms are proposed for intercellular communication through exosomes. The main mechanisms are stimulation of immune system cells such as B cells and dendritic cells and fusion of exosomes and transfer of its content to recipient cells. Exosomes are able to induce significant ROS production through the trigger of calcium signaling [45]. In-vitro studies have indicated that exosomes including cytokines and HMGB1, are able to induce inflammatory responses in bystander cells [45, 46]. micro-RNA (miRNAs) acts as mediators that, through exosomes, are able to initiate bystander effect through epigenetic changes [47]. Transfection of mir-21 through exosomes is a mechanism for stimulation of ROS production and superoxide dismutase (SOD) suppression in non-irradiated cells [48].

2.3. Cytokines Mediated Inflammation and Tissue Injury

Inflammatory cytokines have a potent link to radiation-induced carcinogenesis. Increased levels of inflammatory cytokines after exposure to radiation have been revealed in several studies. Amount and profile of releasing cytokines are dependent on the type and numbers of dead cells. The number of dead cells increases as radiation dose increases. Moreover, necrosis to apoptosis ratio is more obvious with increasing radiation dose. Although cell death through necrosis stimulates secretion of inflammatory cytokines (e.g. IL-1, IL-6, IL-33, TNF-α), apoptosis promotes tolerogenic responses through stimulation of secretion of anti-inflammatory cytokines (e.g. TGF-β, IL-10) [49-51]. Elevated levels of both inflammatory and anti-inflammatory cytokines in irradiated and non-irradiated lung tissue have been observed in previous studies [52, 53]. Increased production of these cytokines results in overproduction of ROS, NO-, prostaglandins etc., that play a central role in acute and late effects of radiotherapy in normal tissues [54]. Migration of secreted cytokines from irradiated area to distant tissues can cause some responses similar to irradiated tissues. However, the pattern of secretion of cytokines is different between irradiated and non-irradiated tissues [53].

2.4. Ionizing Radiation Induced DNA Oxidation and Damage in Carcinogenesis

Free radical production caused by the interaction of ionizing radiation with water molecules and redox mediated biological pathways are responsible for oxidative DNA damage and cell death following exposure to X or gamma rays. Interaction of free radicals with DNA causes formation of different types of DNA oxidation in both nucleus and mitochondria. Oxidation of DNA and also cell death through necrosis or apoptosis can stimulate inflammatory responses and oxidative stress, leading to further DNA damage. Oxidized cell free DNA is elevated in cancer patients and also patients undergoing radiotherapy for their malignancies [55-57]. Among various types of oxidized DNA damage, 7,8-dihydro-8-oxoguanine (8-oxoG) lesion is one of the most important forms of DNA oxidation. Thus, OGG1 is primarily responsible for the 8-oxoG removal, a mutation in this gene having indicated that the following exposure can amplify formation of oxidized DNA [58, 59]. Several studies have demonstrated that the release of oxidized DNA has a role in bystander effect. Exposure of bystander cells to oxidized free DNA results in $ROS^{\cdot}$, reactive hydroxyl radical (ROH) and reactive nitrogen species (RNS) (NO^{-}, peroxonitrite ($ONOO^{-}$)) (Fig. **1**).

2.5. miRNAs in Radiation and Carcinogenesis

miRNAs are a group of non-coding RNAs including 21 to 23 nucleotides. This non-coding RNAs regulate many protein coding genes through targeting and silencing of especial mRNAs. The miRNAs levels change in stress conditions and affect factors associated with carcinogenesis such as proliferation, cell death, metabolism and also tumor suppressors or oncogenes [60, 61]. Change in miRNAs function was shown in several malignancies, such as lung cancer, thyroid, prostate, breast, colorectal, liver, lymphoma, and pancreas [62]. Studies have been showing that the expression of miRNAs is dependent on tissue type and age [63, 64].

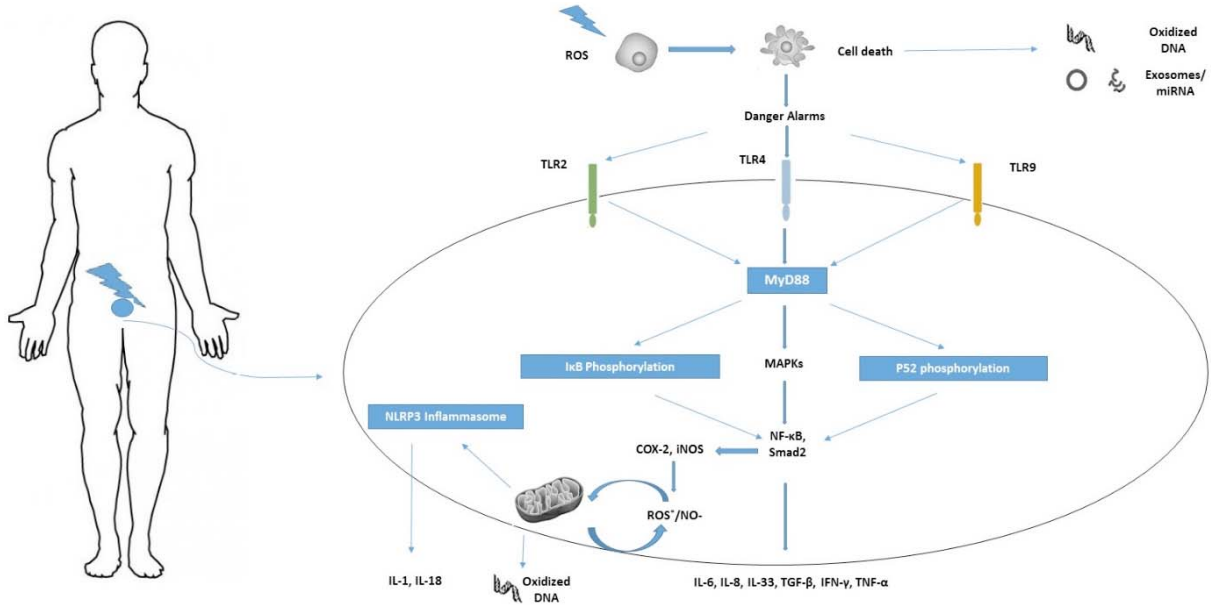

Fig. (1). Radiation interaction with cells causes release of multiple interacting factors including ROS˚, RNS˚, ROH˚, inflammatory cytokines, oxidized DNA, miRNA and exosomes. Although interaction with DNA is the main reason for release of exogenous clastogenic factors, while the interaction with organelles such as lysosome, membrane and mitochondria may also be involved.

Moreover, following exposure to ionizing radiation, the expression of miRNAs occurs in tissue- and sex-specific manners [65, 66]. The basic mechanism involved in the expression of a specific miRNA following irradiation remains unknown, however, increased level of miRNAs is dependent on radiation dose and increase in ROS production [67]. Although there is no direct relationship between radiation dose and numbers of upregulated or downregulated miRNAs, some studies have proposed a relation between radiation damage and change in some serum levels of miRNAs [68-70]. Increased or decreased serum levels of miRNAs can stimulate upregulation or suppression of important genes related to carcinogenesis in different tissues as a tissue-specific manner.

2.6. DNA Damage Responses in Radiation-Induced Inflammatory Responses

In addition to cell death, damage to genetic content off cells stimulates inflammatory responses [71]. DNA damage response (DDR) plays a key role in various pathologies such as chronic inflammation and carcinogenesis. DDR is including some different signaling pathways, including homologous recombination (HR), Non-homologous end joining (NHEJ), mismatch repair (MMR), single-strand break repair (SSBR), base excision repair (BER) and nucleotide excision repair (NER). Although the complete interrelations between DDR and inflammation remain to be elucidated, studies proposed that innate immune system and DNA damage repair have a potent effect on each other [72]. Maybe the best example is interrelations between DDR and NF-κB. There are several studies which indicated that DDR can stimulate regulation of NF-κB, and NF-κB is necessary for stimulation of DNA damage repair. NF-κB stimulates HR through changes in cell cycle, as well as through activation of p53, BRCA1 and RAD51 [73]. On the other hand, DNA damage stimulates upregulation of inflammatory responses via activation of NF-κB in a positive feedback loop [74, 75].

Studies proposed that DDR plays an important role in the detection of fragmented DNA in the cytoplasm. Some DNA damage repair enzymes such as Ku70 and the DNA dependent protein kinase (DNA-PK) can stimulate inflammatory responses after detection of fragmented DNA. For example, Ku70 and DNA-PK which are involved in the initiation of NHEJ can stimulate the production of interferon (IFN) and IL-1 [76, 77]. Also, Rad50 which plays a key role in the repair of double strand breaks via contribution in complex of MRN (Mre11, Rad50 and NBS1) is involved in the upregulation of NF-κB and secretion of IL-1 [78]. The Poly(ADP-ribose) polymerase-1 (PARP-1) is another enzyme that has some roles in apoptosis, cell cycle and DDR [79]. This enzyme stimulates regulation of NF-κB and some inflammatory cytokines such as TNF-α and IL-6 [80].

3. BYSTANDER EFFECTS/NON-TARGETED EFFECTS MEDIATED MECHANISMS THROUGH SEVERAL SIGNALING CASCADES

3.1. Clastogenic Factors Regulation-Modulation in Radiation Carcinogenesis and Radiotherapy

The evaluation of people that have been exposed to high doses of ionizing radiation caused by nuclear disaster or radiotherapy indicates the presence of clastogenic factors [81, 82]. These factors are able to cause breakdown in DNA structure and the resulting mutagenesis that may increase the risk of secondary malignancies [83, 84]. In-vitro studies have shown that serum derived from exposed individuals is capable of inducing mutation in healthy cells. Analysis showed abnormal upregulation of factors involved in Reduction-Oxidation (Redox) system [85, 86]. Although, complete mechanisms remained unknown, in-vitro and in-vivo studies have shown the role of various factors that may be released from irradiated cells, eventually affecting the normal function of non-irradiated cells in distant tissues [82, 85, 87].

Some studies have confirmed the increased level of some clastogenic factors in serum levels of irradiated peoples. Also, irradiation can downregulate some serum levels of factors involved in the regulation of carcinogenesis process. Based on studies that have been conducted so far, it seems that immune system mediators and miRNAs have two important factors. Increased serum levels of several inflammatory and also some anti-inflammatory cytokines have been seen in patients after they had undergone radiotherapy. The level of change in these cytokines has a direct relation to toxicity level in irradiated tissues.

Exposure to radiation changes profile of factors involved in epigenetic modulation of carcinogenesis such as exosomes and miRNAs. An in-vivo study has shown that exposure to radiation causes upregulation of serum level of miR-33, miR-152, miR-199a, miR-744 that affect bystander tissues [88]. Although some of these miRNAs including miR-33, miR-152 have tumor suppressor activity, miR-199a and miR-744 are thought to play a key role in the promotion of some malignancies such as nasopharyngeal, gastric and lung cancer [89-92].

On the other hand, upregulation of some miRNAs such as mir-21 involved in oncogenic process has been revealed in targeted and non-targeted tissues and also in serum level of irradiated patients [93-95]. Upregulation of mir-21 has been observed to be associated with some malignancies such as non-small cell lung carcinoma, glioma and breast cancer [96-99].

It seems that local irradiation causes upregulation or downregulation of several miRNAs that are involved in oncogenic process. Upregulation of miRNAs increases serum levels of them that affect the expression of target genes in non-irradiated tissues. Moreover, downregulation of miRNAs with tumor suppressor properties may increase the activity of oncogenes in distant tissues. Nonetheless, it highly depends on tissue and tumor genesis. However, increased level of some miRNAs such as mir-21 may result in some other mediators including TGF-β.

3.2. NF-κB Regulation and Functions and Radiation

NF-κB belongs to a family with most important transcription factors regulating the expression of a large number of genes involved in cellular processes, such as inflammatory responses, cellular growth, developmental processes and apoptosis. NF-κB is negatively regulated by IkB proteins. A sheer number of evidences have shown an increased expression of NF-κB in both directly irradiated and bystander cells. NF-κB plays a key role in the upregulation of ROS and NO-producing enzymes, including COX-2, iNOS and NADPH Oxidases [100]. Inhibition of NF-κB has shown a decrease in COX-2 and iNOS gene expression in both directly irradiated and bystander cells [101]. Lam *et al.* showed the regulation of N-kB in irradiated cells is crucial for bystander response in non-irradiated cells [102]. This may indicate that NF-κB is necessary for initiation and secretion of clastogenic factors from irradiated cells. On the other hand, clastogenic factors such as inflammatory cytokines are able to stimulate the expression of NF-κB and redox system in bystander cells.

3.3. Lysosomes Functions and Radiation

Lysosomes are intracellular organelles containing acid hydrolyases in their lumen. The acid hydrolyases within this organelle serving as the degradative agent for the autophagy processes. The acidic pH of hydrolyases such as proteases, esterases, DNase IIα, phosphatases, nucleases and etc. are able to degrade a wide variety of molecular targets including DNA structure [103]. Recent studies have demonstrated that defective autophagy mediated by lysosomal enzymes leads to accumulation of DNA damage in cells [104, 105]. Exposure to radiation and production of ROS can induce lysosomal permeability and release of DNase Iiα and acid sphingomylinase [106]. The role of these enzymes in chromosome aberration and cell death has been indicated previously [107, 108]. Also, acid sphingomylinase is involved in radiation induced apoptosis through the activation of ceramide synthase [109, 110]. Bright *et al.* evaluated lysosomal changes in direct irradiated and bystander human fibroblast cells following irradiation. Their results showed a significant lysosomal damage and permeability during 24 hours post irradiation in both irradiated and bystander cells. As well as this result showed that lysosomal changes have direct relation to ROS level [111].

3.4. Protein Kinases and Epigenetics in Radiation Bystander Effects Interactions

Protein kinases are the largest enzyme family involved in cell signal transduction [112, 113]. So far more than 500 different types of protein kinases have been identified based on biochemical studies and human genome sequencing [114]. Protein kinases regulate many fundamental cellular processes through catalyzing the transfer of the phosphate group from an ATP molecule (as a source of energy in cells) to serine, tyrosine or threonine residues in proteins [115]. Protein kinases work in concert with intersecting signaling cascades to regulate various vital cell processes such as cell growth, metabolism, division, apoptosis and motility. So, disruption of protein kinases signaling can have profound effects on cell fate. Abnormal regulation of protein kinases has been seen in a broad range of cancers [116, 117].

The role of protein kinases in different responses to ionizing radiation such as radiosensitivity, apoptosis, etc., has been detected [118, 119]. The role of some protein kinases in bystander effect has been revealed. Based on the studies that have been conducted so far, mitogen-activated protein kinases (MAPKs), protein kinase B and protein kinase C are involved in ROS production and oxidative damage in bystander cells.

3.4.1. Mitogen Activated Protein Kinases (MAPKs) Functions and Radiation Bystander Effects Interactions

MAPKs, a group of protein kinases, play a pivotal role in regulating gene expression in response to extracellular signals such as mitogens, cytokines, growth factors and others. MAPKs control basic cellular processes such as stress responses, survival, differentiation, proliferation, migration, growth and apoptosis [120, 121]. The best-known genes among MAPKs are p38 isoform, the extracellular signal-regulated kinases 1 and 2 (ERK1/2) and c-Jun amino-terminal kinases (JNKs). Exposure to alpha particles cause rapid phosphorylation of ERK1/2, c-Jun, and p38 and their downstream proteins in bystander human fibroblasts cells. The activation of MAPKs and downstream proteins attenuated SOD or catalase suggesting that superoxide and hydro-

gen peroxide are involved in the activation of MAPKs, and subsequent chromosome aberrations in bystander cells [122]. Additionally, both ERK and JNK, but not p38 pathways are shown as activated and key bystander effected proteins in HPV-G cells. Calcium ions released from the endoplasmic reticulum play a key role in this pathway [123].

3.4.2. Protein Kinase B (PKB) Functions and Radiation Bystander Effects Interactions

The role of Protein Kinase-B (Akt) in resistance of cells to radiation induced apoptosis has been analysed previously [124]. Akt is involved in the formation of micronuclei (MN) in bystander affected cells. They showed rapid phosphorylation of Akt that caused activation of mammalian target of rapamycin (mTOR) pathway in non-irradiated cells. Also, they showed the activation of Akt/mTOR independent of nucleus DNA damage in irradiated cells. The results indicated that the exposure of cytoplasm to ionizing radiation or free radicals is responsible for DNA damage in bystander cells [125].

3.4.3. Protein Kinase C (PKC) Functions and Bystander Effect Interactions

Protein Kinase Cs (PKCs) have basic roles in many intracellular processes, including cell survival, regulation of cell cycle, differentiation, apoptosis etc. PKC including family kinases are classified into sub-families according to activation mechanisms. Conventional PKC isoforms (cPKC) include PKCα, βI, βII and γ, the novel PKC (nPKC) is composed of PKCδ, PKCε, PKCθ and PKCη, and the atypical PKC (aPKC) isoforms are PKCζ and PKCι [126]. The activation of PKC in response to stress situations such as exposure to radiation has been demonstrated in various studies [127, 128]. The role of some isoforms of PKC in bystander cells has been confirmed. Translocation of PKCα from cytosol to the cell membrane is involved in ROS production and oxidative damage in bystander cells. It has been shown that upregulation of PKCα amplifies the amount of the TNFR1 on the cell membrane that results in increased expression of ERK and COX-2, and mutagenesis in bystander cells [129]. Activation of PKCα is related to other transcription factors such as NF-κB, MAPKs and inflammatory cytokines such as TNFα, IL-6. Also, this PKC isoform potentiates cytokine secretion by macrophages through stimulation of TLR4 and TLR2 [130].

Hu *et al*. showed that PKCε gene is upregulated by 3-fold in the human primary fibroblast cells after co-culture with cells irradiated by α-particles. Further analyses showed that upregulation of PKCε is involved in DNA damaged bystander cells [131]. Although the downstream signaling for this pathway was not detected, it is possible that the activation of TNFα, ERK and other downstream genes such as COX-2 was involved in bystander effect signaling through PKCε [132-134].

The expression of some other isoforms of the PKC was evaluated, including PKC-βII, PKC-α/β and PKC-θ in the bystander human lung fibroblast cells. The results showed up-regulation of all three isoforms of PKC in bystander cells [135]. The role of these isoforms of PKC in the promotion of COX-2 gene expression and carcinogenesis has been confirmed [136, 137]. It seems that COX-2 is the main downstream enzyme as a source of ROS production and DNA damage for different types of PKC in bystander effect and affected cells.

3.5. Toll-like Receptor 9 (TLR9)

As discussed previously, cellular exposure to radiation induces oxidized DNA and exosomes. In addition to stimulation of inflammatory responses from irradiated cells, these mediators can directly migrate to non-irradiated cells and stimulate ROS production. Exosomes released from irradiated cells has the capability to increase the amount of ROS and double strand DNA breaks but not NO- in bystander cells. Analyses showed that ROS production is dependent on TLR9 signaling pathway [138]. TLR9 on bystander cells can detect exosomes and oxidized DNA which stimulate ROS˚ production [139, 140]. Based on several studies, it has been observed that TLR9 through NF-κB pathway is responsible for ROS production after exposure to oxidized DNA or exosomes [141-144].

3.6. Epigenetic Regulation of Cell Cycle, miRNA, DNA Methylation, Oncogenes and Radiation Bystander Effect Interactions

Some studies have shown deregulation of miRNAs associated with cell cycle, apoptosis and DNA hypomethylation in non-targeted tissues. Local irradiation causes down-regulation of miR-23a and miR-23b in both male and female and also down-regulation of miR-24 in the male. These changes paralleled an increase in the expression of p38 and CXCL12 protein. Down regulations of miR-23 and miR-24 cause upregulation of CXCL12. This cytokine is able to induce secretion of cytoplasmic Ca^{2+}. In in-vitro studies, Ca^{2+} flux was observed in bystander cells and rapid Ca^{2+} flux was found to be involved in oxidative DNA damage [9].

Upregulation of mir-16 as a suppressor of Bcl-2 in bystander cells is involved in cell apoptosis. The overexpression of Bcl-2 contributes to the malignant phenotype in some malignancies such as chronic lymphocytic leukemia. On the other hand, upregulation of the miR-29 family that targets MCL1 may sensitize bystander cells to apoptosis. These changes are associated with increased apoptosis. Additionally, some changes in miRNAs expression may be due to the upregulation of c-MYC. c-MYC is a proto-oncogene which controls proliferation, cell cycle and apoptosis. c-MYC causes upregulation of miR-17 and -20a that stimulates cell proliferation [145].

Upregulation of oncogenes such as c-MYC may be related to hypomethylation due to DNA damage and suppression of DNA methyltransferases (DNMT) expression. Local irradiation of a limited area can cause hypomethylation in distant non-irradiated tissue. Local brain irradiation causes downregulation of DNMT1, DNMT3a and DNMT3b in spleen. However, persistent hypomethylation is due to suppression of DNMT3a. miRNAs analyses have been shown that overexpression of miR-194 in non-irradiated spleen is responsible for this. miR-194 can target both DNMT3a and MeCP2 [7] (Fig. **2**).

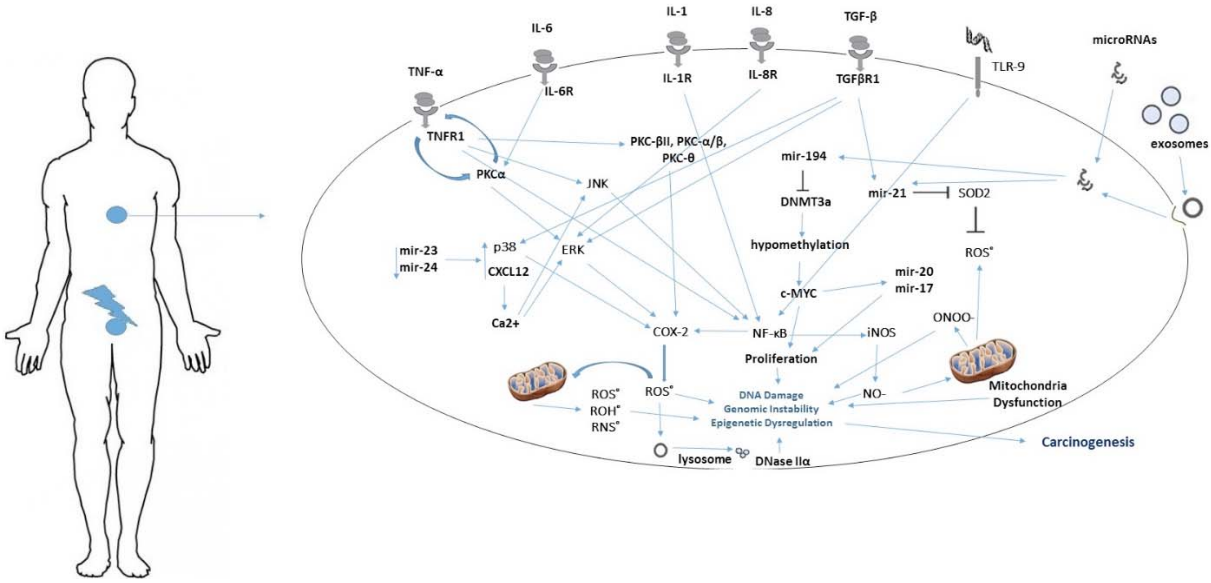

Fig. (2). Signaling pathways involved in DNA damage and genomic instability in non-targeted tissues. Although, complete mechanisms of this phenomenon remain to be known, illustrated signaling pathways are tissue-specific manner, and all of these signalings are not observed in all tissues. The most important factors for DNA damage include ROS, ROH and RNS, $NO^{\cdot}$, $ONOO^{\cdot}$, while other factors such as lysosomal enzymes, cytokines, exosomes and miRNAs are involved in oxidative stress. Mitochondria generated free radicals ROS, RNS$^{\circ}$ and ROH propagate the bystander-effect mediated injury at the affected cellular, tissue and organs. Additionally, exosomes and miRNAs may increase thr risk of radiation carcinogenesis without DNA damage.

4. TISSUE AND SEX DEPENDENT BYSTANDER RESPONSES

A series of experiments has reported the role of tissue and sex in DNA damage and inflammatory responses in both targeted and non-targeted cells and tissues. Evidences have shown that patterns of radiation-induced mutation and subsequent gene expression and epigenetic changes, as well as second malignancies occur at different frequencies in males and females [146-149]. Korturbash *et al*. showed that local cranial irradiation of mice results in a sex-dependent and tissue dependent induction of DNA damage and alterations in global DNA methylation. They showed that although non-targeted effect can cause permanent hypomethylation in the spleen, this effect has not been investigated for skin. Also, their result indicated that hypomethylation is more obvious for male rather than female [150]. Similar results have been observed for the regulation of microRNAome and inflammatory responses in non-targeted tissues [151, 152].

5. LET DEPENDENT BYSTANDER RESPONSES

Similar to direct irradiated cells, response of bystander cells is different for various types of radiations. However, the pattern of this responses may be different. In a study evaluating the formation of micronuclei for different quality of radiations including X-ray, carbon, neon and argon ions, results indicated that the number of micronuclei in bystander cells is more for higher LET [153]. The evaluation of bystander signaling markers in human lymphocytes co-cultured with macrophages showed that heavy carbon ions or γ-rays can increasingly upregulate MAPKs in bystander cells compared to α-particles [154]. *In vivo* studies are need to confirm these funding.

SUMMARY AND CONCLUSION

Although complete mechanisms of bystander effects and non-targeted effects need further elucidation to have solid practical applications that can be of benefit in cancer diagnosis and radiotherapy applications, studies conducted so far show the complexity of multiple factors and their radiation interactions in radiation-induced bystander effects and non-targeted effect to various cellular, molecular and tissues and organ(s) targets. In-vitro and in-vivo experimental studies have shown that the main exogenous clastogenic factors secreted from irradiated cells consist of cytokines, exosomes, miRNAs, protein kinases, as well as oxidized DNA that are critically involved eventually in the upregulation or downregulation of affected genes and proteins, and epigenetic regulation. Interestingly, secretion of some of these factors may have no direct and/or indirect relationship to nuclear DNA damage. These factors are released from irradiated cells, tissues and organs into the bloodstream, and are affected by field organs, thus appropriately termed as bystander effects and non-targeted effects based on a biophysical phenomenon. The most important observed effects of these factors are free radicals generation, cytokines generation, inflammation, kinases activation, upregulation or downregulation of genes and enzymes and their activities in Redox system, increased mitochondria activity, and dysregulation of antioxidant proteins activity in bystander effect targeted cells, tissues and organ systems. In addition to the direct and indirect actions of ROS, ROH$^{\circ}$ and RNS$^{\circ}$ free radicals mediated DNA breaks and mutations, they are able to hypersensitize the mitochondria, and the lysosomal membrane as targets. Free radicals-induced DNA break results in epigenetic hypomethylation and upregulation of some oncogenes including c-MYC, Ras and exosomes. Additionally, miRNAs may directly suppress DNA methyltransferases and

maintenance of hypomethylation. On the other hand, upregulation of some oncogenes, and also TGF-β causes activation of other miRNAs that may amplify genomic instability in bystander cells, tissues and organs. All of these dynamic changes involved in describing radiation mediated bystander effects and non-targeted effects can only be viewed as a complex multifactorial phenomenon of cellular functions, genomic instability and radiation carcinogenesis, and the approach to and outcome to radiotherapy. Future discoveries and advancements in the understanding of radiation driven bystander effects and non-targeted effects will impact future utility for better understanding of radiation carcinogenesis, radiotherapy of cancer, effects on target and non-targeted tissues and organs, and their significance in targeted and non-targeted injury sites, and in the same milieu. Potential side applications of bystander effects and non-targeted effects for novel treatment modalities and therapeutics discoveries that can enhance protection and treatment of normal cells, tissues and organs from targeted cancerous cells, tissues and organs must also eventually be explored. Applications to other diseases to include acute and degenerative diseases novel treatment and therapeutics strategies can potentially be an off-shot adaptation and application of an in-depth understanding of bystander effects for disease pathologies. Eventual discoveries of novel therapeutics that can target the molecular signature of radiation mediated bystander effects and non-targeted effects must be achieved for advancement of the impact of such phenomenon for radiation carcinogenesis and radiotherapy strategies advancements.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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